THIN-FILM PERIPHERAL NERVE ELECTRODE

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1.0 BACKGROUND

A program to develop a functional neuromuscular system (FNS) capable of graded and stable activation of hand muscles for the restoration of grasp in quadriplegic individuals is being undertaken. The objective of the program is the development of a thin film neural cuff electrode and the demonstration of the efficacy of the electrode for grasp in an *in vivo* study using a raccoon model.

Specific features of the proposed electrode include:

- multiple, independently addressable charge injection sites that will facilitate implementation of established and emerging stimulation protocols such as anodal field steering and anodal blocking;
- leads and electrodes are vacuum deposited on a planar, monolithic fluorocarbon substrate that is flexible and avoids bulky interconnects in close proximity to the implantation site;
- charge injection electrodes of Pt or activated iridium oxide (AIROF), both of which are stable under the anticipated charge injection protocols;
- fluorocarbon substrates that can be thermoformed into a self-sizing cuff to allow a snug but elastic fit to the nerve.

The circumneural electrodes are fabricated by vacuum depositing metal films on thin sheets of fluorocarbon polymer and photolithographically patterning and the leads and charge injection sites. The patterned substrate is then thermally sealed with a second polymer layer to electronically isolate the leads from the physiological environment. The charge injection sites are exposed by a combination of photolithography and ion or plasma etching of vias through the polymer overlayer. Once all planar fabrication processes, i.e., photolithography, vacuum deposition, and etching have been completed, the electrode is cut out of the substrate and the desired cuff and lead geometries created by thermoforming.

An example of an electrode in planar geometry prior to thermoforming the cuff is shown in Figure 1. The leads and charge injection sites are patterned on a large polymer substrate with the leads extending to a bonding pad located several centimeters from the cuff. Four charge injection sites, designed to evaluate anodal steering, are shown on the cuff.

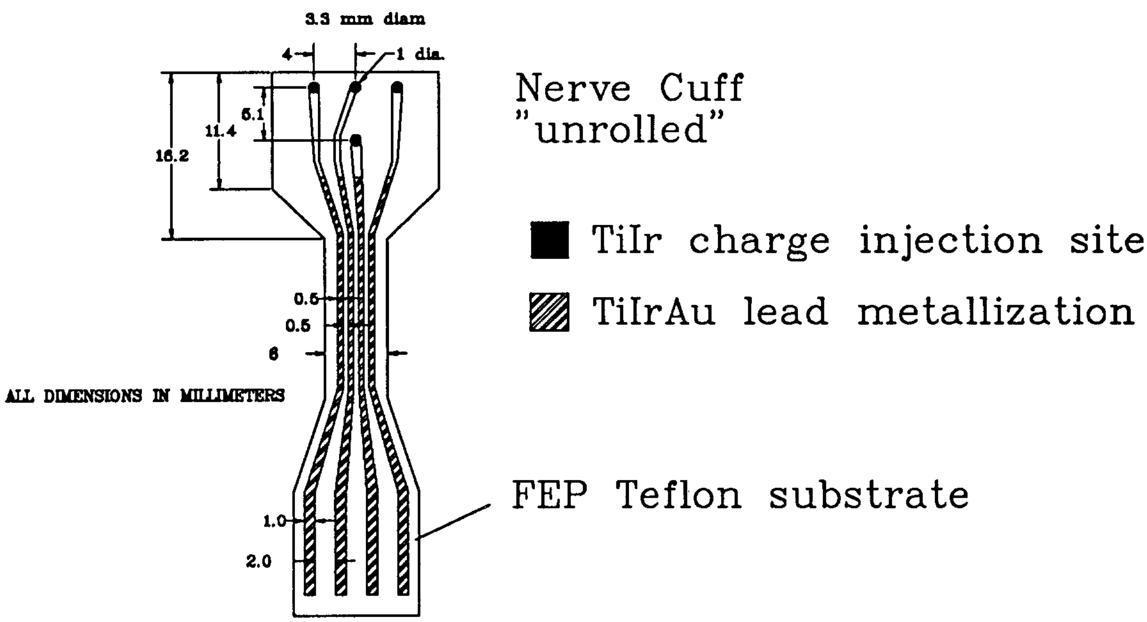

Figure 1. A circumneural cuff having four charge injection sites in a geometry suitable for evaluating anodal steering.

2.0 TECHNICAL PROGRESS

During the second reporting period, the methods for metallizing the cuff electrodes were revised to improve adhesion and long-term stability of the TiIr and TiIrAu films. Issues related to adhesion, availability, and wettability of the insulation on the interior surface of the cuff were also addressed.

2.1 Procedures for Metallization of Cuff Electrodes

FEP Teflon, with a thickness of 0.002 inches remains the substrate material of choice. Prior to metallization the substrate is cleaned following the procedure described in Table 1.

Table 1. Procedure for cleaning FEP Teflon prior to metallization.

Step 1	Immerse 5 minutes in H_2SO_4:H_2O_2; 2:1; H_2O_2 is 30% by weight
Step 2	Rinse in deionized H_2O
Step 3	Dry with cleanroom grade towels (polymer based)

The cleaned FEP Teflon is taped onto ITO-coated glass. The ITO is electrical conductive and acts as an electrode for substrate biasing during deposition of the initial Ti adhesion layer. The substrates are plasma cleaned in oxygen for 15 minutes using a low power barrel reactor. The plasma treatment enhances the adhesion and flow characteristics during spinning of the photoresist used to define the pattern of the metallization. The photolithography procedure is outlined in Table 2.

Table 2. Procedure for photolithographic patterning.

Photoresist	Shipley 1818 microposit (positive resist)
Spin conditions	3500 rpm for 25 seconds
Soft Bake	30 minutes at 100^{0}C
UV exposure	4 seconds (Oriel illuminator)
Developer	Shipley CD-30 developer for 45 seconds
Rinse	flush with deionized H_2O

A pin connector is attached to the ITO coating on each glass substrate holder using silver epoxy with a second, nonconductive epoxy overlayer to shield the Ag from the plasma. Insulated wires are then attached to each substrate for bias sputtering. Prior to metallization, the substrates are subjected to an *in vacuo* anneal and plasma cleaning following the conditions in Table 3.

Table 3. *In vacuo* precleaning procedure.

Substrate mounting	substrates mounted 6.5 cm from sputter targets
Initial pumpdown	chamber pumped to low 10^{-6} torr range
Thermal anneal	during pumpdown substrates heated 10 min. at 90-120°C and held for 15 minutes at 125°C
Plasma clean	O_2 plasma clean each substrate at 10 watts RF, 10 sccm O_2, 10 millitorr pressure, for 2 minutes
Repump	chamber pumped to low 10^{-6} torr range

A thin layer of Ti is applied with a RF substrate bias to aid in adhesion at the metal-Teflon interface. To promote even coating and minimize damage to the substrates from energetic bombardment during bias sputtering, this initial deposition is done with the substrate moving through a short arc beneath the sputtering gun. The remaining metallization is deposited without a substrate bias. Interfaces between subsequent metal layers are compositionally graded to improve adhesion. Deposition conditions for the metallization are detailed in Tables 4-6.

Table 4. Sputter procedure for Ti adhesion layer on FEP Teflon.

Gas pressure	10 millitorr Ar
Flow rate	10 sccm
DC power	150 mA current, 300-310 V target bias
Substrate bias	5 W RF (13.56 MHz)
Presputter time	10 minutes
Deposition time	6 minutes

Following deposition of the Ti adhesion layer, the chamber is vented to atmospheric pressure with dry nitrogen and the electrical leads for substrate biasing disconnected. A Ti/Ir bilayer is then deposited over the entire area of the cuff using the conditions described in Table 5.

Table 5. Sputter procedure for Ti/Ir bilayer on the Ti adhesion layer.

Base pressure	low 10^{-6} torr
Gas pressure	10 millitorr Ar
Flow rate	10 sccm
DC power	150 mA total current (Ti and Ir)
Presputter time	10 minutes
Deposition time	6 minutes
Rotation	105 rpm

Details of the procedure for grading the Ti and Au interface are provided in Triannual Report No. 1 (April 1994). Following deposition of the Ir, the chamber is vented to atmosphere and the area of metallization that will be used as a charge injection sites is masked with a thin glass microscope slide. A Ti/Au bilayer is deposited over the remaining metallization to reduce the resistance of the lead lines. The deposition conditions for the Ti/Au are provided in Table 6. The overall sequence of metals in the coating is the following:

charge injection site: FEP-Teflon/Ti(w/bias)/TiIr graded interface/Ir;

lead metallization: FEP-Teflon/Ti(w/bias)/TiIr graded inteface/Ti/TiAu graded interface/Au.

Table 6. Sputter procedure for Ti/Au bilayer on Ir.

Base pressure	low 10^{-6} torr
Gas pressure	10 millitorr Ar
Flow rate	10 sccm
DC power	150 mA total current (Ti and Au)
Presputter time	10 minutes
Deposition time	6 minutes
Rotation	105 rpm

Photoresist and unwanted metallization is removed by liftoff using acetone. Light mechanical abrasion or ultrasonic agitation is occasionally necessary to remove all the residual resist.

2.2 Inner Surface Insulation

As originally proposed, the insulation on the inner surface of the cuff electrodes was a thin, spun film of Teflon AF. The coating and etching conditions developed for the Teflon AF are detailed in Tables 7 and 8, respectively. This material will probably not be available for applications involving chronic implantation. Therefore, several alternative materials based on silicone polymers are being evaluated. These include materials such as NuSil Med-6605 and NuSil Med-1137 (Nusil Silicone Technology, Carpinteria, CA).

Table 7. Teflon AF coating procedure.

Spin solution	Teflon AF and Florinert mixed 1:2
Spin rate	1500 rpm
Time	25 seconds
Prebake	5-10 minutes at 110°C
Presputter time	10 minutes at 150°C
Repeat application	first 5 steps
Final bake	1 hour at 150°C

Following application of the Teflon AF, the charge injection sites are open by plasma etching. An aluminum plate (0.0625 in thick) with appropriately positioned through-holes is used as a mask to protect the remainder of the Teflon AF. The etching conditions are listed in Table 8.

Table 8. Teflon AF etching procedure.

Etching gas	92% O_2: 8% CF_4
Pressure	500 millitorr
Temperature	100°C
RF Power	200 watts 13.56 MHz
Time	20 minutes

2.3 Thermoforming

The cuff is formed in the coated FEP sheet by annealing in an aluminum mold at 135°C. The operation is performed in an autoclave with H_2O present. The H_2O in the "steam annealing" process is to improve heat transfer and is not thought to modify the properties of the FEP Teflon (e.g. act as a plasticizing agent). The cuffs are autoclaved for 30-40 minutes. After autoclaving, the cuffs and mold are quenched in cold water.

2.4 Electrolyte Wetting.

Electrochemical evaluation of the charge injection sites following cuff formation revealed an unanticipated phenomenon that could effect the performance of the electrodes. The inner surface of the cuff was sufficiently hydrophobic that the PBS/CBS mixed-buffer electrolyte would not wet the interior of the cuff, preventing electrochemical characterization. Whether the hydrophobicity of the inner cuff surface will compromise the stimulation performance remains to be determined.

In order to improve the wettability of the inner surface, the Teflon AF lining was treated in a methanol/hydrogen plasma. A PECVD system was used for the plasma treatment. The conditions are described in Table 9. The plasma treatment was effective in making the surface of the Teflon AF partially hydrophilic as qualitatively judged from the contact angle of H_2O droplets. The effect of the treatment, however, was temporary and the surface returned to its original hydrophobic condition after about 30 minutes of air exposure. FEP Teflon samples treated in the same manner retained their hydrophilic surface.

Table 9. Process conditions for plasma treatment to improve wettability.

Etching Gas	CH_3OH/H_2
Pressure	500 mTorr
Temperature	100° C
RF Power	200 Watts
Time	30 minutes

2.5 Cyclic Voltammetry and Charge Injection

Electrode sites that were exposed to electrolyte by uncurling a cuff could be evaluated by cyclic voltammetry and charge injection. The Ir sites for this investigation were not activated. Figure 2 shows a cyclic voltammogram of a 1 mm diameter electrode on a cuff with design shown in Fig. 1. The electrolyte was a mixed carbonate and phosphate buffer with levels of NaCl and buffer concentration similar to that of interstitial fluid. During voltammetry at a sweep rate of 50 mV/s, 1100 $\mu C/cm^2$ of charge were transferred on each half-cycle.

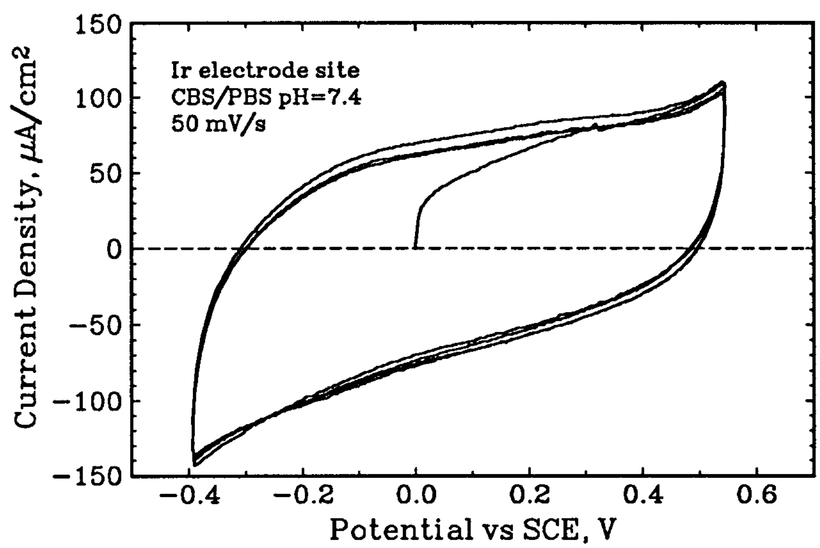

Figure 2. Cyclic voltammetry of an Ir charge injection site on an FEP Teflon cuff (uncurled) in a CBS/PBS electrolyte at 50 mV/s.

A monophasic, constant-current, cathodal protocol was used for charge injection studies. Charge-balance was achieved by the discharge of an 0.2 μF capacitor in series with a 10 Ω current measuring resistor and the electrochemical cell. The capacitor discharge was accomplished by electronically shorting the output of the stimulator 20 μs after the cathodic pulse phase. A schematic diagram of the charge injection circuit is shown in Fig. 3. The potential transients during charge injection were recorded with a digital oscilloscope in the AC coupled mode. A high input impedance electrometer was used to measure the open-circuit corrosion potential and the interpulse potential (IPP). In our test protocol, the IPP is measured as the average potential during pulsing as recorded by the analog electrometer. Since the pulse and capacitor discharge phases are only ~1% of the interpulse period, they do not significantly effect the IPP measurement. We find this method introduces less error than direct measurement with an oscilloscope in the DC mode, since the oscilloscope has a comparatively low input impedance. Following each potential transient measurement during the charge injection studies, the stimulation circuit was disconnected from the electrochemical cell and the open-circuit potential (V_{oc}) of the electrode was measured with the electrometer after allowing two minutes for the potential to stabilize.

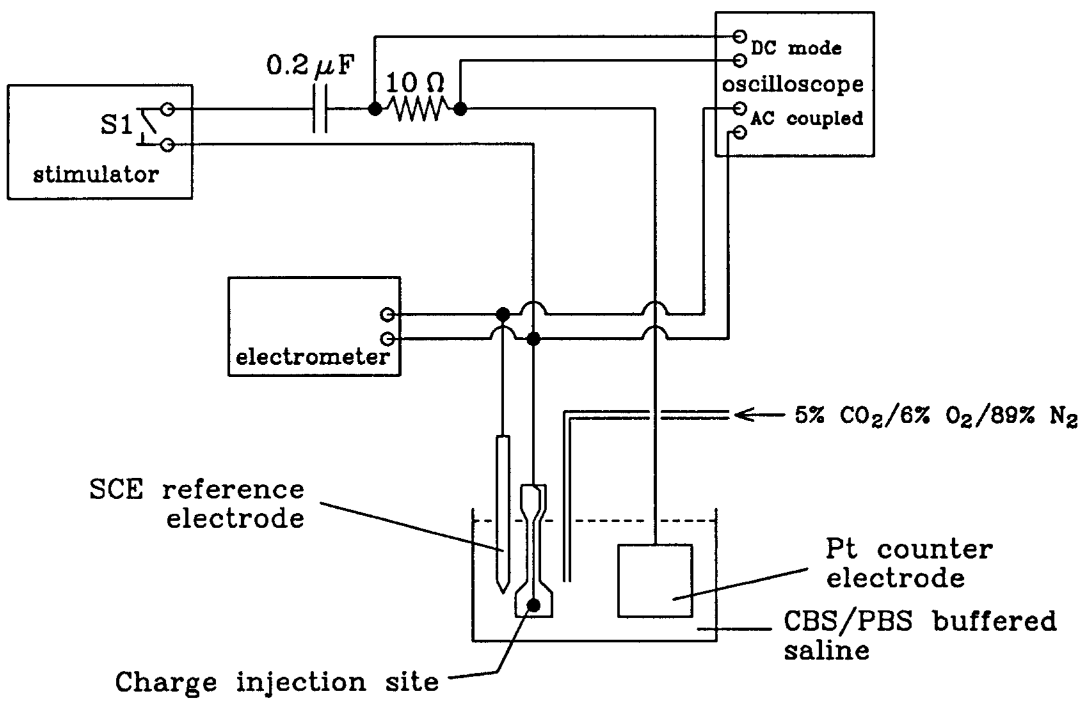

Figure 3. Experimental setup for charge injection studies.

Each of the four electrode sites on the cuff were evaluated by potential transient measurements at different current levels. The data are reported in Table 10. In these short-term experiments, 100 μC/cm^2 could be injected at the Ir sites. The maximum current level employed, 8 mA, is well above the maximum anticipated for *in vivo* studies, suggesting that, for at least the acute evaluation of selectivity and gradation, that activation to AIROF is unnecessary. The access resistance, which should be as low as possible for electrodes in fully implanted systems, varied from 470 to 989 Ω. A similar evaluation of the charge injection response was performed using only the Ir electrodes. The two outer members of the tripole were externally shorted and used as a counter electrode while the inner electrode was driven with the negative pulse. Using a 5 mA current, the access resistance determined from the measured compliance voltage of the stimulator was only 200 Ω. This resistance value is lower than that obtained with remote Pt counter electrode and SCE reference electrodes. Since solution resistance does not generally contribute a significant portion of the access resistance the lower impedance is thought to result from electrolyte leakage between the FEP Teflon substrate and Teflon AF insulation.

Table 10. Ir electrode charge injection on FEP Teflon cuff with large area Pt counter electrode.

Electrode	Current	Charge	I_{pp}	$E_c$max	V_{oc}	Access Res.
	mA	μC/cm^2	V (SCE)	V (SCE)	V (SCE)	Ω
CF8A	8	102	0.6	-0.44	0.35	700
CF8B	7.2	92	0.35	-0.61	0.15	989
CF8C	3.6	45	-0.06	-0.54	0.2	470
CF8D	2.4	31	-0.08	-0.6	0.28	717

3.0 *IN VIVO* STUDIES

Progress Report #2: Thin-Film Peripheral Nerve Electrode

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3.1 Abstract of *In Vivo* Studies

We have proposed that complex hand movements might be obtained with direct median nerve stimulation through an implanted multielectrode nerve cuff. We expect to show that selective stimulation of digits can induce a graded response. In addition, the direct nerve stimulation should induce repeatable hand responses and result in no injury to the nerve.

3.2 Progress on *In Vivo* Studies

3.2.1 Animal Model

A video tape has been made of the dissection of the cadaver raccoon forearms indicating muscles of the forearm. Major digit flexors such as flexor digitorum superficialis and flexor digitorum profundus, and extensor muscle of the digits of the extensor digitorum communis have been identified for EMG electrode implantation.

Selective responses of forearm muscles to median nerve stimulation will depend upon the structure of the median nerve. We observed clear fasicular demarcations in the median nerve within the upper arm of the raccoon. We could trace many of these fascicles to specific muscles. Thus, selective activation of one or two muscles should be possible using graded stimulation. Because of marked fasicularization we should also expect that we could activate different muscles with stimulation in different quadrants of the nerve. The raccoon median nerve is easily accessible within the upper forearm. It courses for a short length within the upper arm close to the skin giving easy access for our nerve cuff.

3.2.2 Methods for Evaluating EMG, Paw and Digit Movement

Considerable effort has been expended during this project in developing recording techniques. A recording platform has been constructed in our model shop that will hold the arm and allow free digit movement. Force transducers have been procured and connected to our recording system. EMG recording systems have been set up. The implantable stimulator has been received and is being evaluated for selectivity studies.

3.2.3 Sensory Recording

A comparison protocol to study the use of this cuff to access the somatosensory system was devised. The protocol is as follows:

1. Procedures to investigate the usefulness of the nerve cuff as a somatosensory prosthesis will be carried out in each animal after successful completion of the motor testing component.
2. The somatosensory testing will in many ways mimic the motor testing procedures.
3. The receptive fields of each of the 12 electrodes in the cuff will be mapped by using fine von Frey-like filaments selectively applied to the various hand skin surfaces innervated by the median nerve (It is expected that only coarse differences, if any, will be seen).
4. A craniotomy will be performed on the side opposite the cuff electrode, and a small window cut in the dura to expose the digit area of the first somatosensory area. The cortex will be kept moist with warmed mineral oil.
5. The first somatosensory area will be mapped using a multi-unit metal electrode. Light touch stimuli to the appropriate digit will be used as the adequate stimulus.
6. The cortical mapping will be repeated with the stimulus being the stimulation of individual electrodes in the cuff, then the stimulation of pairs of electrodes. The cortical locus of peak evoked multi-unit activity to each stimulus will be identified (it is expected that only coarse differences, if any, will be seen).
7. The mapping described in #6 will be repeated, but this time steering currents will be used to achieve selective activation of portions of the median nerve.
8. The responses and maps from the various tests (motor and sensory) will be compared.

4. FUTURE WORK

In the next reporting period, efforts will focus on characterizing the electrochemical response of cuff electrodes. Areas that will require particular attention are the effectiveness of polymer insulation on the inner surface of the cuffs and electrical (ionic) isolation of individual metal traces under the insulation. Silicone-based polymers are being evaluated in place of the Teflon AF originally proposed. The major difficulty we foresee with the use of silicones is adhesion to the FEP Teflon. We are currently investigating plasma treatments of the Teflon to encourage adhesion and also the use of small perforations in the cuff to allow silicone precursor penetration through the thickness of the Teflon.